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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,387	SEN ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *5,14,24 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-13,15-23,25-27 and 29-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5-9-05, 8-29-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 6-20-08.

Claims 1-36 are pending in the instant application.

Election/Restrictions

Claims 5, 14, 24, 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6-20-08.

Applicant's election without traverse of species encompassed by claim 4 (sensor switch from first conformation to second conformation when an analyte binds), claim 7 (aptamer), claim 13 (switch region is located proximate to receptor site), claim 23 (charge flow inducer is an oxidizing agent in an excited state), and claim 27 (sensor is a conductor) in the reply filed on 6-20-08 is acknowledged.

Information Disclosure Statement

The information disclosure statement filed 5-9-05 fails to fully comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because some of the references listed do not contain full citations (e.g. lacking periodical volume numbers, dates of publication). It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for

purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

The references with complete citations have been considered, but the references lacking full, proper citations have not been considered. The references that have not been considered, and those references that have been considered are indicated in the completed IDS forms attached hereto Appropriate correction is suggested. (Please see, e.g., sheet numbers 2, 3, 4, 6 of the IDS filed 5-9-05).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-13, 15-23, 25-27, 29-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn compositions and methods of detecting the presence of any analyte comprising providing at least one analyte sensor comprising first, second, third and fourth oligonucleotide stems which are multi-stranded DNA helices, connected together at either a three way or a four way junction, and wherein at least one of the

first, second, and third stems comprises a non-Watson-Crick base pairing in the vicinity of the three way junction, and/or optionally comprising a fourth oligonucleotide stem, which four stems are connected together at a four way junction, and further comprising a receptor site which optionally binds adenosine and which site is operatively connected to the first oligonucleotide and second oligonucleotide stems and capable of binding the analyte, which sensors are alterable between conformational states, wherein a first conformational state substantially impedes charge transfer between the two oligonucleotide stems, and, upon binding of an analyte to the receptor site (which is proximate to a switch region and which switch region comprises unpaired nucleotide in a first conformational state), the sensor switches from an unexcited, unoxidized conformational state which impedes charge transfer, to one where a charge flow inducer becomes an excitable moiety in an oxidized state and forms an oxidizing agent, and which moiety is optionally rhodium III or anthraquinone, and which analyte sensor further comprises a detector which is a conductor electrically coupled to one of the oligonucleotide stems, and whereby the charge flow inducer triggers charge flow in one of the oligonucleotide stems, and a change is detected in charge transfer by electrically coupling a detector to the other one of the sensor stems, and changes are detected in the absence and presence of an analyte by measuring formation of oxidation products of the sensor, optionally including heating the sensor in the presence of piperidine and separating reaction products by gel electrophoresis.

The specification and claims do not adequately describe the very broad genus comprising these analyte sensors. This broad genus encompasses a vast array of

molecules and combination of subunits or component parts, and the disclosure fails to provide a representative number of species for the very broad genus which provide for the functions claimed, of detecting any analyte, and which sensor or sensors produce a signal upon converting to an excited, oxidized state upon a conformational change.

The specification and claims do not adequately describe the concise structural features (e.g. polynucleotide sequences, structures of all component parts of the analyte sensor constructs) that distinguish structures within the broadly claimed genus from those without. The specification teaches schematics of mixed or composite sensors, and some examples of analyte sensors able to detect adenosine binding by adenosine specific aptamers, and utilizing guanine doublets to monitor charge transfer to the sensor and detector stems of adenosine sensors.

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species, requisite sequences, structural components, or higher order structures to describe the very broad genus comprising at least one analyte sensor comprising first, second, third and fourth oligonucleotide stems which are multi-stranded DNA helices, a receptor site which optionally binds any analyte and which site is operatively connected to the first oligonucleotide and second oligonucleotide stems and capable of binding any analyte, which sensors are alterable between conformational states, wherein a first conformational state substantially impedes charge transfer between the two oligonucleotide stems, and, upon binding of any analyte to the receptor site, switches from an unexcited, unoxidized conformational state which impedes charge transfer, to one where a charge flow inducer becomes an

excitable moiety in an oxidized state, and which provides for the function of detecting any analyte. The description provided in the instant disclosure does not adequately describe the elements, structures or sequences required for the broad genus claimed.

Thus, one of skill in the art would reasonably conclude that Applicant was not in possession of the broadly claimed genus.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6-13, 15-23, 25-27, 29-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanton et al (US 2003/0087239) and Breaker (Current Opinion in Biotech., Vol. 13, pages 31-39, 2002) in view of the combined teachings of

Meade et al (USPN 6,238,870), Berner et al (USPN 6,144,869), and Gasper et al (J. Am. Chem. Soc, Vol. 119, pages 12,762-12,771, 1997).

The claims are drawn compositions and methods of detecting the presence of an analyte comprising providing at least one analyte sensor comprising a first, second, third and fourth oligonucleotide stem, connected together at either a three way or a four way junction, and wherein at least one of the first, second, and third stems comprises a non-Watson-Crick base pairing in the vicinity of the three way junction, and/or optionally comprising a fourth oligonucleotide stem, which four stems are connected together at a four way junction, and further comprising a receptor site which optionally is an aptamer which binds adenosine and which is operatively connected to the first oligonucleotide and second oligonucleotide stems, which sensors are alterable between conformational states, wherein a first conformational state substantially impedes charge transfer between the two oligonucleotide stems, and, upon binding of an analyte to the receptor site (which is proximate to a switch region and which switch region comprises unpaired nucleotide in a first conformational state), the sensor switches from an unexcited, unoxidized conformational state which impedes charge transfer, to one where a charge flow inducer becomes an excitable moiety in an oxidized state and forms an oxidizing agent, and which moiety is optionally rhodium III or anthraquinone, and which analyte sensor further comprises a detector which is a conductor electrically coupled to the oligonucleotide stem, and whereby the charge flow inducer triggers charge flow in one of the oligonucleotide stems, and a change is detected in charge transfer by electrically coupling the detector to one of the sensor stems, and changes are detected in the

absence and presence of adenosine by measuring formation of oxidation products of the sensor, and/or optionally including heating the sensor in the presence of piperidine and separating reaction products by gel electrophoresis.

Stanton et al (US 2003/0087239) teach methods of detecting an analyte comprising providing at least one analyte sensor (*a.k.a.* biosensor), or a plurality of smaller sensors forming an array of sensors (*e.g.*, on a semiconductor) comprising a first, second, third and fourth oligonucleotide stem, connected together at either a three way or a four way junction, and wherein at least one of the first, second and third stems comprises a non-Watson-Crick base pairing in the vicinity of the three way junction, and/or optionally comprising a fourth oligonucleotide stem, which four stems are connected together at a four way junction, and further comprising a receptor site which optionally is an aptamer and which is operatively connected to the first oligonucleotide and second oligonucleotide stems, which sensors are alterable between conformational states, and, upon binding of an analyte to the receptor site (which is proximate to a switch region and which switch region comprises unpaired nucleotide in a first conformational state), the sensor switches from one conformational state to a second conformational state which elicits a detectable signal, reflecting analyte binding. Stanton teaches biosensor reagents comprising a first and second nucleic acid stem, and a target molecule activation site comprising a structure which specifically interacts with a target molecule and a signaling unit. Generation of a signal by the signaling moiety is sensitive to the conformational changes in the nucleic acid sensor molecule which occurs upon allosteric activation of the target molecule activation site by a target

molecule. The invention taught by Stanton makes use of a molecular switch which is activated upon binding of a target to a nuclei acid molecule, including an aptamer specific for a target molecule. The analyte detectors of Stanton include the binding of a target molecule by the sensor, resulting in changes in both the conformation and the physical aspect of the nucleic acid sensor molecule, wherein conformational changes in the nucleic acid sensor molecule upon target binding will modify the chemical environment of the signaling moiety, and whereby changes in the physical aspect of the nucleic acid sensor molecule will alter the kinetic properties of the signaling moiety, and these will lead to a detectable change in the detection properties of the nucleic acid sensor molecule (see esp. the abstract, figures 2, 3, 5, 6, 9-12, 15 and 16; pages 1-6, 13, 16; claims 1-3, 8, 11, 57).

Breaker (Current Opinion in Biotech., Vol. 13, pages 31-39, 2002) teaches allosteric nucleic acids for analyte detection comprising a first, second, third and fourth oligonucleotide stem, connected together at either a three way or a four way junction, and wherein at least one of the first, second and third stems comprises a non-Watson-Crick base pairing in the vicinity of the three way junction, and/or optionally comprising a fourth oligonucleotide stem, which four stems are connected together at a four way junction, and further comprising a receptor site which optionally is an aptamer which binds adenosine, and which is operatively connected to the first oligonucleotide and second oligonucleotide stems, which sensors are alterable between conformational states, and, upon binding of an analyte to the receptor site (which is proximate to a switch region and which switch region comprises unpaired nucleotide in a first

conformational state), the sensor switches from one conformational state to a second conformational state which elicits a detectable signal, reflecting analyte binding (see entire document, esp. figures 1, 3 and 5).

These primary references of Stanton and Breaker do not teach the sensor switches changing, upon analyte binding to the receptor site, from an unexcited, unoxidized conformational state which impedes charge transfer, to one where a charge flow inducer becomes an excitable moiety in an oxidized state and forms an oxidizing agent, and which moiety is optionally rhodium III or anthraquinone, and which analyte sensor further comprises a detector which is a conductor electrically coupled to the oligonucleotide stem, and whereby the charge flow inducer triggers charge flow in one of the oligonucleotide stems, and a change is detected in charge transfer by electrically coupling the detector to one of the sensor stems, and changes are detected in the absence and presence of adenosine by measuring formation of oxidation products of the sensor, and/or optionally including heating the sensor in the presence of piperidine and separating reaction products by gel electrophoresis.

Meade et al (USPN 6,238,870) teach the design, synthesis and use of nucleic acids as bioprobes, which bioprobes comprise charge flow inducers coupled to the nucleic acid molecules, which inducers include rhodium III, which functions as an oxidizing agent in an excited state, and which nucleic acid molecule further comprises a conductor, and which charge transfer is detected by coupling a detector to the nucleic acid molecule. Meade teaches the use of charge flow inducers, including rhodium, for

enhancing the sensitivity of nucleic acids as bioprobes (see esp. the abstract; col. 1-5; 7-10; 12-14; 27 and 28).

Berner et al (USPN 6,144,869) teach methods and devices for measuring analytes comprising biosensors and sensor elements that monitor electrical signals correlating with the concentration of a chemical compound, and which devices include a sensing electrode that converts an analyte or its derivative to an electrical signal. Berner teaches the use of rhodium as a conductor, which is optionally part of the biosensor system for converting an analyte or its derivative to a detectable electrical signal. Berner teaches the detection of electrochemical signals from the generation of a current which is proportional to the amount of analyte which is reacted (see col. 17, 18, 20, 22, claims 1, 3, 5, 20).

Gasper et al (J. Am. Chem. Soc, Vol. 119, pages 12,762-12,771, 1997) teach the use of piperidine to generate strand breaks in DNA, which DNA has been derivatized with anthraquinone. Gasper teaches the predictable chemical reaction of piperidine with anthraquinone derivatized DNA to compare DNA strand break patterns for use in comparing electrophoretic patterns between different DNA samples (see the abstract and introduction on page 12,762-3; bridging paragraph on pages 12,763-4; figure 3 on page 12,765).

It would have been obvious to use allosteric nucleic acid biosensors previously taught by Stanton and Breaker, and further comprising rhodium for increasing the detection of analytes in a solution because the use of allosteric biosensors was well known in the art to reduce the background for detecting analytes, as illustrated by

Stanton and Breaker, and rhodium was well known in the art to increase the sensitivity of analyte detection because Meade teaches the use of charge flow inducers, including rhodium, for enhancing the sensitivity of nucleic acids as bioprobes and Berner teaches the use of rhodium as a conductor, which is optionally part of the biosensor system for converting an analyte or its derivative to a detectable electrical signal.

One of skill in the art would have been motivated to utilize rhodium in such allosteric biosensors because rhodium was well known to conduct current and increase the sensitivity of nucleic acid probes when the current it conducts gets converted to an electrical signal. One of ordinary skill would have expected that the design and use of allosteric biosensors covlalently modified with rhodium would provide for increased analyte sensitivity because the derivatization of nucleic acids with rhodium was well known in the art, as taught previously by Meade, and the conducive properties of rhodium were well known in the art, as taught previously by Berner, and the advantages of converting an analyte to an electrical signal using rhodium was known to provide for enhanced biosensitivity of sensors comprising rhodium. One would have been motivated to utilize anthraquinone modified nucleic acids as biosensors because it was well known in the art that anthraquinone derivatized DNA reacts reliably with piperidine to generate DNA strand breaks, especially under oxidizing conditions, as taught previously by Gasper. One of skill in the art would have been motivated to use this approach to generate samples from the DNA biosensors to compare their footprinting patterns following their strand breaks, to compare the different biosensors for their ability to bind analytes.

One of ordinary skill in the art would have expected that applying the conjugation and chemical reactions taught previously by Meade and Gasper to the allosteric biosensors previously taught by Stanton and Breaker, would produce a more sensitive way of detecting analyte binding to biosensors, especially after converting the analyte binding signal to an electric signal, using the teachings of Berner.

For these reasons, the instant invention would have been obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6-13, 15-23, 25-27, 29-36 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-43

of copending Application No. 12/102,669. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to compositions and methods of detecting the presence of any analyte comprising providing at least one analyte sensor comprising first and second oligonucleotide stems, and further comprising a receptor site which binds an analyte, and which site is operatively connected to the first oligonucleotide and second oligonucleotide stems and capable of binding the analyte, which sensors are alterable between conformational states, wherein a first conformational state substantially impedes charge transfer between the two oligonucleotide stems, and, upon binding of an analyte to the receptor site (which is proximate to a switch region and which switch region comprises unpaired nucleotide in a first conformational state), the sensor switches from an unexcited, unoxidized conformational state which impedes charge transfer, to one where a charge flow inducer becomes an excitable moiety in an oxidized state and forms an oxidizing agent.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the

Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE CO PIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
10-9-08

/Jane Zara/
Primary Examiner, Art Unit 1635